REMARKS

Applicants have received and reviewed the Office Action dated July 16, 2009. By way of response, Applicants have amended claims 1, 2, 16, 17, 19, 22, 27 and 30. No new matter has been added. Claims 1-4, 6-9, 14-19, 21-25 and 27-31 are pending. Applicants submit that the amended claims are supported by the specification as filed.

Claim 1 has been amended to introduce the limitations of claim 2 therein. Claim 27 has been amended to recite "swelling multilayered system". Support for this recitation in claim 27 can be found throughout the specification as filed including at least page 9, line 22-23, which reads "In one illustrative embodiment according to the invention a swelling and expanding system is employed."

For the reasons presented below, Applicants respectfully submit that the amended claims are in condition for allowance, and notification to that effect is earnestly solicited.

Objection to Claims

The Examiner objected to Claim 22 for a minor informality. The spelling of "pregelatinised" pointed out by the examiner has been revised as suggested to "pregelatinized". Accordingly, Applicants request withdrawal of this objection.

Rejection of Claims under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 2 and 21 under 35 U.S.C. 112, first paragraph. The Examiner objected to certain terms employed in these claims. Applicants respectfully traverse this rejection.

The Office Action objected to the recitation in claim 2 of "24 hours" and "prolonged." The amended claims do not include the terms objected to in the Office Action.

Claim 2 has been combined into claim 1 and amended claim 1 hence reads to "d. a swelling enhancer; wherein the swelling agent in combination with swelling enhancer, swell in the presence of gastric fluid such that the size of the dosage form is sufficiently increased to not pass through the pylorus, thereby providing retention of the dosage form in the stomach of a patient."

Further, claim 2 has been amended to read "....wherein the dosage form is retained in the upper gastrointestinal tract for a time period of up to about 12 hours." Support for this recitation can be found at page 16, lines 13-16 as "Following oral administration to a patient, the dosage form is retained in the upper gastrointestinal tract for a time period of about 30 min to about 12 hours or about 1 hour to about 9 hours or most preferably about 1 hour to about 6 hours".

Further, the Examiner objected to the term "functionalized polystyrene" in Claim 21 and states there is no support for this limitation in the originally filed specification. In view of this the Applicant's respectfully submit that the claim be examined in view of the amended specification as filed in response to the office action dated January 23, 2009. As required by the Examiner the substituted specification includes changes in representation of terms that are trademarks. The substituted specification included no new matter and the claims hence be examined with respect to the same.

Accordingly, Applicants respectfully submit that the amended claims fully comply with §112, first paragraph, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 16-19 and 30 under 35 U.S.C. §112, second paragraph. The Examiner noted an error in the dependence of these claims.

The Examiner objected to claims 16-19 since the limitation "hydrophilic polymer" has insufficient antecedent basis. Further, the Examiner objected to claim 30 since the limitation of "said disintegrant" again has insufficient antecedent basis. The dependence of each of these claims has been corrected to provide appropriate antecedent basis.

Accordingly, Applicants respectfully submit that the amended claims fully comply with §112, second paragraph, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 3, 4, 6-9, 14, 15, 18, 19, 21, 24 and 25 under 35 U.S.C. § 102(b) as being anticipated by Falk et al. (US 4803081). Applicants respectfully traverse this rejection.

Amended claim 1 includes the subject matter of claim 2, which was not subject to this rejection. Accordingly claim 1 and its dependent claims are free of this rejection. Claim 1 now recites that the controlled release composition is a gastroretentive system.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited reference does not anticipate the presently claimed compositions, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims under 35 U.S.C. § 103

1. The Examiner rejected claims 2, 16, 17, 22 and 23 under 35 U.S.C. § 103 as obvious over Falk (US 4803081) in view of Shell (US 5972389) and Patel (US 2003/0180352). Applicants respectfully traverse this rejection.

The Falk et al. Reference

Falk et al. disclose an extended release preparation of an active compound with very low solubility containing the active compound dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer (abstract). Falk et al. further disclose the object of their invention is to provide a preparation of a drug with very low solubility that shows prolonged and nearly constant rate of drug absorption for a long period of time and concurrently maintains a high extent of bioavailability.

Falk et al. disclose that the object of the invention is achieved by using a solubilizer which is mixed with the drug with very low solubility. Falk et al. further state that the active compound is preferably dissolved or dispersed in the solubilizer. In solution the drug is said to be included in a micellar structure formed by the solubilizer. The mixture of the drug and the solubilizer is incorporated into a pharmaceutical formulation, which gives prolonged release. According to Falk et al. the solubilized drug is preferably combined with a hydrophilic gel system, namely a hydrophilic swelling matrix. This controlled release form is as per Falk et al. a suitable way to control the release of the micelles of drug and solubilizer. Falk et al. further disclose that the major part of the hydrophilic gel system has a viscosity below 100cps.

Such a hydrophilic system with a viscosity below 100 cps cannot lead to retention of the dosage form disclosed in the stomach. This indicates that the preparation of Falk et al. is not intended to be a gastroretentive system wherein the size of the dosage form on swelling in the

presence of gastric fluid is sufficiently increased to not pass through the pylorus thereby providing retention of the dosage form in the stomach.

Selection of appropriate viscosity grades of hydrophilic swelling agents is a prerequisite to the designing of a gastroretentive dosage form. Specific grades of swelling agents or such swelling agents together with swelling enhancers are employed to cause sufficient swelling and subsequent gastroretention. The instant invention discloses controlled release gastroretentive swelling system incorporating a solubilized drug. The controlled release gastroretentive swelling system according to the present invention employs a combination of polymers, which swell voluminously in the presence of gastric contents to increase the dosage form size such that it precludes its passage through the pylorus.

Thus, though the Examiner discusses the components of the extended release preparation of Falk et al. and relates it to the components of the instant invention, the Applicants respectfully submit here that these components of Falk et al. and their percentages employed may seem comparable, but the low viscosity swelling components employed by Falk et al. fail to produce gastroretentive systems that are disclosed via the instant invention.

The present invention discloses and enables controlled release gastroretentive oral pharmaceutical compositions of therapeutically effective amount of one or more pharmacologically active agents showing low bioavailability wherein solubilized drug when incorporated in gastroretentive system leads to increase in solubility and release of drug near the absorption site thereby providing better absorption of the drug and increased bioavailability. Thus solubilization combined with gastroretention as disclosed in the instant invention provides increased bioavailability and extended release which further leads to reduction in dose, dosage frequency, improved patient compliance and more importantly enhanced therapeutic benefits.

Therefore, Applicants respectfully submit that the Falk et al. reference neither teaches nor suggests the presently claimed invention, and that the shortcomings of this reference are not remedied by the secondary references.

The Secondary References Do Not Remedy the Shortcomings of the Falk et al. Reference

According to the Office Action, the difference between the rejected claims and Falk et al. is that Falk et al. does not expressly disclose a gastric retentive dosage form, the swelling agent polyethylene (oxide) or the swelling enhancer the cross-linked polyvinylpyrrolidone. That is, the

Falk et al. reference fails to teach or suggest any inventive features of the presently claimed invention. The Office Action states that the deficiency in the swelling agent poly (ethylene oxide) is cured by Shell et al. and the deficiency in the swelling enhancer cross-linked polyvinylpyrrolidone is cured by the disclosure of Patel et al.

Shell et al. disclose controlled release dosage forms that comprise a tablet or capsule containing a plurality of particles of a solid-state drug dispersed in a swellable/erodible polymer that (i) swells unrestrained dimensionally via imbibition of gastric fluid to increase the size of the particles to promote gastric retention within the stomach of a patient in which the fed mode has been induced, (ii) gradually erodes over a time period of hours, with the erosion commencing upon contact with the gastric fluid, and (iii) releases the drug to the stomach and duodenum at a rate dependent on the erosion rate. Once ingested, the tablet or capsule of Shell et al. disintegrates to disperse the particles within the stomach where they imbibe water to cause them to swell and promote retention in fed-mode-induced patients. As the gastric-retained particles gradually erode, the drug is released in a controlled manner to the stomach for treatment of local disorders, and to the upper gastrointestinal tract where it becomes available for absorption in a controlled and therapeutic manner. Thus, the dosage form of Shell et al. is multiparticulate type of a gastroretentive system and not a monolithic or multilayered matrix type of gastroretentive system.

In contrast to controlled-release dosage form of Shell et al. comprising a plurality of solid particles or pellets of a solid-state drug dispersed within a polymer which upon ingestion rapidly dissolve or disintegrate upon contact with the gastric fluid to permit the particles to disperse in the stomach; the compositions of the present invention are monolithic or multilayered matrix systems, which upon ingestion as recited in amended claim 1 cause swelling of the entire dosage form that is then retained upon swelling in the upper gastrointestinal tract. Gastroretentive systems as of Shell et al. comprising plurality of particles tend to undergo faster gastric emptying than the compositions of the present invention that are retained in the upper gastrointestinal tract for longer times.

Thus though Shell et al. utilizes a polymer like poly (ethylene) oxide, it does not disclose or suggest the design of monolithic or multilayered matrix type gastroretentive systems using the same that are retained in the upper gastrointestinal tract for a prolonged time. Further a person skilled in the art would not see any suggestion in the disclosure of Shell et al. which relate to

system comprising plurality of particles to design monolithic or multilayered matrix type of gastroretentive systems. Therefore, Shell et al. when combined with Falk et al. do not in any manner disclose or suggest the compositions of the presently claimed invention. The present invention combines gastroretention and solubilization such that a delicate balance between release of the drug from the dosage form and gastroretention is maintained and an increase in bioavailability is assured.

Patel et al. discloses solid pharmaceutical compositions for improved delivery of a wide variety of active ingredients contained therein or separately administered that include a solid carrier being formed of different combinations of active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides and solubilizers. Patel et al. is directed to providing solid pharmaceutical compositions having a more rapid dissolution upon administration to a patient. Patel et al. does not in any manner discuss any swelling or gastroretentive type of a dosage form and further includes cross-linked polyvinylpyrrolidone in its laundry list of additives. Such a listing of cross-linked polyvinylpyrrolidone has been linked without any specificity to its use in the compositions of the present invention. Patel et al. in fact does not in any manner disclose or suggest design of gastroretentive systems and further in combination with Falk et al. alone or with Falk et al. and Shell et al. do not even suggest the compositions of the instant invention.

Accordingly based on the foregoing differences, Applicants respectfully submit that the cited references neither teach nor suggest the presently claimed compositions and withdrawal of this rejection is earnestly solicited.

2. The Examiner rejected claims 27-31 under 35 U.S.C. § 103 as obvious over Falk (US 4803081) in view Doshi et al. (US 2003/0232081). Applicants respectfully traverse this rejection.

Amended claim 27 recites that the composition is in the form of a "swelling multilayered system". The Doshi et al. reference discloses a floating bilayered system. Thus the Doshi et al. reference in combination with the Falk et al. reference does not disclose or suggest the compositions of amended claim 27.

According to the Office Action, the difference between the rejected claims and Falk et al. is that Falk et al. does not disclose a multi-layered expanding gastric retentive dosage form or the swelling enhancer cross-lined polyvinylpyrrolidone. Further, the Office Action states that the

deficiencies in a multi-layered expanding gastric retentive dosage form and the swelling enhancer cross-linked polyvinylpyrrolidone are cured by the disclosure of Doshi et al..

In view of this rejection Applicants respectfully submit that the differences between Falk et al. and the instant invention discussed above with respect to anticipation rejections are applicable in this context as well.

Further, Doshi et al. disclose a controlled release multilayer composition that is capable of delivering a first active agent from one layer immediately followed by continuous controlled delivery of second active agent from matrix forming layer while the dosage form floats and is retained in the fluid of the environment. The floating system of Doshi et al. includes an immediate release layer containing one active agent and a disintegrating agent while a second floating matrix forming layer includes a gas generating component, a gelling agent, and a second active agent.

Doshi et al. further disclose that their composition on oral ingestion, comes in contact with gastric fluid and the first layer disintegrates rapidly releasing the active ingredient instantaneously and the second layer swells and gels in presence of fluid of the environment resulting in volume expansion entrapping the gas generated by the reaction of gas generating component and fluid of the environment, thus, releasing the active agent from second layer which may be same or different, in a controlled manner while the system floats in gastric environment. Thus compositions of Doshi et al. require both swelling and gas generation for gastric retention.

The second layer of the composition of the Doshi et al. comprise of gas generating component which generates gas on contact with gastric fluid and is selected from group of water soluble carbonates, sulfites and bicarbonates such as sodium carbonate, sodium bicarbonate, sodium metabisulfite, calcium carbonate. This gas generating component upon interaction with gastric fluid generates carbon dioxide or sulfur dioxide that gets entrapped within hydrated gel matrix of the gelling agent. This indicates that Doshi et al. though relying on gas generation for achieving floatation of the dosage forms, the composition of Doshi et al. include only the gas generating component and do not include any acid source, thereby being dependent entirely on the natural gastric acid levels in the stomach for generating gas for floatation. Levels of such natural gastric acid are highly variable, depending on fed or fasting states. This dependency on the gastric acid levels can in instances lead to failure of this mechanism of achieving desired

floatation of the dosage form. Further the matrix forming gelling agent present in the second layer of the compositions of Doshi et al. are present in an amount of about 5% to about 20%, more preferred being 7.5% to 15% and the most preferred being 10% by weight based on the total weight of the composition.

In contrast, the compositions of the present invention rely primarily on swelling as the mechanism for desired gastroretention and employ biocompatible swelling agents along with swelling enhancers to achieve the same. The weight percent of the biocompatible swelling agent in the dosage form is about 5 to about 90%, preferably about 10 to about 70 weight percent, and most preferably about 15 to about 50 weight% of the composition. Thus the matrix forming gelling agents of Doshi et al. are preferably incorporated at a lower amount in the composition, indicative of the dependence of this system of Doshi et al. mainly on gas generation that also has higher chances of failure. Moreover, the gelling agents of Doshi et al. are incorporated to balance such a failure of the mechanism of gas generation for gastroretention. Thus, variability in achieving floatation of the dosage forms of Doshi et al. even though gelling agents are present is possible.

Furthermore the dosage forms of Doshi et al. may be coated with a polymeric film to provide protection from moisture. This coating is meant to impart moisture barrier properties to increase stability of the compositions. To prevent any gas generating reaction from occurring under standard conditions this need to have moisture protective coating arises in Doshi et al.

Unlike, Doshi et al. the controlled release compositions of the present invention mainly rely of swelling to achieve gastroretention. Designing of systems that depend on a single mechanism for achieving gastroretention requires immense efforts and present Applicant's have designed such systems that are not dependent on variable factors such as the gastric acid level for performance of the dosage form. Further the need that exists in Doshi et al. of coating the dosage form as seen in all the enabled examples for protection from moisture is eliminated by the compositions of the present invention and thereby an additional processing step of coating towards the preparation of the compositions is also reduced.

Thus though multilayered systems have been disclosed by Doshi et al, it discloses compositions wherein the second layer achieves gastroretention by relying on two mechanisms i.e. gas generation and swelling that can present variable drug absorption profiles in-vivo, but it

does not in any manner disclose or suggest systems that can achieve gastroretention by relying on a single mechanism as swelling.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited references neither teach nor suggest the presently claimed compositions and withdrawal of this rejection is earnestly solicited.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: 16 Oct '09

Mark T. Skoog
Reg. No. 40,178

MTS:kf

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